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Synthesis of novel 6-substituted sulfur-containing derivatives of pyridoxine

Nikita V. Shtyrlin [a], Roman S. Pavelyev [a], Mikhail V. Pugachev [a], Lubov P. Sysoeva [a], Rashid Z. Musin [b], Yurii G. Shtyrlin [a,*]

[a] Research and Educational Center of Pharmacy, Kazan Federal University, Kazan 420008, Russian Federation
[b] A.E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Centre of the Russian Academy of Sciences, Kazan 420088, Russian Federation

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ABSTRACT

An efficient synthesis of novel 6-substituted derivatives of pyridoxine was achieved. The reactions of various thiols with mono-, bis-, and tris(chlorine) derivatives of 6-methyl-2,3,4-tris(hydroxymethyl)pyridin-5-ol (6-hydroxymethylpyridoxine) gave sulfur-containing derivatives of pyridoxine.

Chemical modification of biologically active compounds of natural origin is one of the most efficient approaches in drug development. A promising starting compound is vitamin B_6 (pyridoxine) which participates in over a hundred enzyme reactions involved in biosynthesis, metabolism, and regulatory functions in living organisms.[1]

A complicated problem in pyridoxine chemistry is its functionalization at C-6. Only a few reports have been published that consider the synthesis of such compounds and their biological activity.[2] In particular, arylazo derivatives act as selective antagonists of $P2X_1$ and $P2Y_{13}$ receptors,[2e,2f] whereas, aminopyridinol derivatives exhibit antioxidant properties.[2g]

Jones obtained 6-hydroxymethylpyridoxine through initial formation of the pyridine ring from ethyl hydroxymethyleneoxalacetate and iminoacetylacetone followed by its functionalization in five steps.[2c,2d] This method was laborious and not effective. Recently, we described an efficient method for the synthesis of 6-hydroxymethylpyridoxine from pyridoxine hydrochloride in three steps.[3]

In continuation of our studies on pyridoxine derivatives, it was interesting (for the first time) to produce thioethers of 6-hydroxymethylpyridoxine via nucleophilic substitution reactions.

Thioethers are an important class of diverse organic compounds that are used widely in medicine,[4] agriculture,[5] and industry.[6] Moreover, thioethers can be used for the asymmetric synthesis of sulfoxides as well as for the production of sulfones.[7]

The most straightforward method for the synthesis of thioethers is based on nucleophilic substitution reactions. In order to involve the hydroxy groups in the reaction they need to be converted into a good leaving group using activating agents such as alkyl- or arylsulfonates.[8] Activation of the hydroxymethyl groups of pyridoxine derivatives was achieved by reaction with thionyl chloride[9] or methanesulfonyl chloride.[10]

We achieved selective activation of the hydroxymethyl groups of 6-methyl-2,3,4-tris(hydroxymethyl)pyridin-5-ol using isomeric six- and seven-membered ketals **1** and **2**, which we obtained earlier in two or three steps from pyridoxine hydrochloride.[11] Chlorination of the hydroxymethyl group of seven-membered ketal **1** by the reaction with thionyl chloride occurred via isomerization of the seven-membered ketal into six-membered derivative **3** with a yield of 62% (Scheme 1). In this case, a large number of by-products formed which is typical for reactions of alcohols with thionyl chloride in the absence of a hydrogen acceptor.[12] Attempts to block isomerization of the seven-membered ketal into the six-membered product with triethylamine or pyridine as the acceptors of hydrogen chloride failed. However, the reaction of six-membered ketal **2** with thionyl chloride occurred under mild conditions and resulted in the desired product **3** in 85% yield.

The lower yield of six-membered ketal **3** in the chlorination reaction of compound **1** in comparison with **2** can be explained by the occurrence of a side process involving dehydrochlorination of the hydroxymethyl group at the *para*-position to the aromatic hydroxy group with the formation of a *p*-quinone methide which participates in different side reactions.[13]

* Corresponding author. Tel./fax: +7 843 233 75 31.
E-mail address: Yurii.Shtyrlin@ksu.ru (Y.G. Shtyrlin).

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